An inventive aspect of the present invention is the combination of *Streptococcus pneumoniae* polysaccharides with protein carriers and not the polysaccharides themselves. The specification teaches that a pneumococcal vaccine containing polysaccharides of 23 serotypes is already commercially available. U.S. Patent 5,623,057 (being applied against the present claims under 35 USC § 103) teaches that there are at least 84 known serotypes of *Streptococcus pneumoniae* based upon their capsular polysaccharides. Thus, the various polysaccharides that comprise a portion of the claimed invention are well known and therefore need not be described further. *Vas-Cath, Inc. vs. Mahurkar*, 935 F. 2d 1555, 1563, 19, USPQ 2d 1116 (Fed. Cir. 1991).

In light of the foregoing, Applicants respectfully request that the rejection of claims 1-24 under 35 U.S.C. § 112, first paragraph, be withdrawn.

Rejections Of Claims 1-24 Under 35 U.S.C §112, Second Paragraph

Claims 1-24 stand rejected under 35 USC § 112, second paragraph, because, according to the Examiner, one skilled in the art would be unable to determine the metes and bounds of a claim limitation which recites "derived from *Streptococcus pneumoniae*". The Examiner is concerned that the claims may encompass unknown modifications to the "protein" (Applicants believe that the Examiner means "polysaccharide"). Applicants respectfully traverse.

The specification amply describes what is meant by the term "derived from." Page 10, lines 26-35 describes that the polysaccharides may be extracted from a microorganism according to conventional methods and purified according to conventional methods. The polysaccharide may be used in its crude form or, alternatively, it may be fragmented in order to obtain the polysaccharide having an average molecular weight less than that of the polysaccharide originally extracted.

Further, page 12, the paragraph beginning at line 10, explains that polysaccharides "derived from" various serotypes were fragmented according to known methods. (see lines 13-16). For coupling to a protein carrier, the polysaccharide is subjected to reductive amination in the presence of sodium cyanoborohydride in order to link a molecule of diaminohexane to a terminal reducing group. The polysaccharide "thus derived" is then activated by a succinimide group. (lines 22-24). In another example, in the same paragraph, the polysaccharide is treated to add hydrazine groups. The polysaccharide "thus derived" is then coupled with the carrier protein in the presence of EDAC.

Given that the specification provides adequate description of how a polysaccharide can be "derived from" any particular serogroup, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 112, second paragraph.

Rejection of Claims 1-9, 12-15 and 24 Pursuant To 35 U.S.C. § 103

Claims 1-9, 12-15 and 24 stand rejected under 35 USC § 103(a) as obvious over Marburg, *et al.* in view of Matuhashi, *et al.* The Examiner understands that Marburg, *et al.* differs from the present claims in that it does not teach a conjugate composition comprising a capsular polysaccharide from *Streptococcus pneumoniae* linked to an additional protein carrier such as Dt or Tt. However, according to the Examiner, Matuhashi, *et al.* teach a process for the production of the composition comprising a biologically toxic substance, such as Dt or Tt, covalently linked to a saccharide to form a substance-saccharide conjugate. According to the Examiner, it would have been *prima facie* obvious to one of ordinary skill in the art to make the conjugate composition comprising the capsular polysaccharide from *Streptococcus pneumoniae* linked to more than one immunogenic carrier proteins such as Dt or Tt. Applicants respectfully disagree.

To establish a *prima facie* case of obviousness, three basic criteria must be met: (1) there must be a teaching or suggestion in the prior art to make the claimed invention; (2) there must be a reasonable expectation of success; and (3) all of the claimed limitations must be taught or suggested in the prior art references. M.P.E.P. § 2143. The teaching or suggestion and the reasonable expectation of success must both be found in the prior art, and must not be based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991); M.P.E.P § 2143.

The Federal Circuit "has recently reemphasized the importance of the motivation to combine . . . ." *Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1343, 56 U.S.P.Q.2d 1641, 1644 (Fed. Cir. 2000). "[B]road conclusory statements regarding the teaching of multiple references, standing alone, are not evidence.'" *Ecolochem, Inc. v. S. Calif. Edison Co.*, 227 F.3d 1361, 1372, 56 U.S.P.Q.2d 1065, 1073 (Fed. Cir. 2000). Instead, "'the showing of combinability must be clear and particular.'" *Ruiz v. A.B. Chance Co.*, 234 F.3d 654, 665, 57 U.S.P.Q.2d 1161, 1168 (Fed. Cir. 2000).

The presently pending claims are not rendered *prima facie* obvious for several reasons. First, all of the elements of the pending claims are not taught in the either Marburg *et al.* or Matuhashi *et al.* Applicants pointed this out in their Response to the previous Office Action and the Examiner has provided no information that rebuts this conclusion in the instant Office Action.

For example, Marburg *et al.* do not teach the linking of the polysaccharide to two or more protein carriers as recited in part (b) of pending independent claim 1. While Matuhashi *et al.* may teach the coupling of a polysaccharide to a biologically toxic substance such as Dt, Matuhashi *et al.* do not teach the coupling of the polysaccharide to *two or more protein carriers*. Thus, every element of the presently pending claims in not taught in the prior art.

Another reason the presently pending claims are not rendered *prima facie* obvious is there is no teaching or suggestion to combine Marburg *et al.* and Matuhashi *et al.* The Office Action points to no motivation or suggestion in either of the references that they should be combined. Instead, after simply summarizing the teaching of Marburg *et al.* and Matuhashi *et al.*, the Office Action states "it would have been *prima facie* obvious to one of ordinary skill in the art ... to make a conjugate composition comprising a capsular polysaccharide from *Streptococcus* linked to more than one immunogenic carrier protein such as Dt or Tt." (See page 6). This is simply a broad, conclusory statement regarding the teaching of the two references and cannot be the basis for a rejection based upon prima facie obviousness. *Ecolochem, Inc. v. S. Calif. Edison Co.*, 227 F.3d 1361, 1372, 56 U.S.P.Q.2d 1065, 1073 (Fed. Cir. 2000). The Office Action fails to provide a showing of a motivation to combine that is clear and particular, which is required to support such a rejection. *Ruiz v. A.B. Chance Co.*, 234 F.3d at 654.

In fact, no such teaching or motivation to combine Matuhashi *et al.* and Marburg *et al.* exists. In the present invention, the polysaccharides of pneumococci were conjugated to the protein carriers to provide an antigen capable of inducing a T-dependent response, most particularly in neonates. (see page 3 of the specification). The polysaccharides are coupled to the protein carriers such as Dt or Tt so that the appropriate immune response will be initiated after immunization. This is different than Matuhashi *et al.* where the protein carriers themselves are the toxins (such as Dt) against which subjects are immunized. Individual toxins are linked to non-toxic polysaccharides to detoxify the

proteins without decreasing their immunogenicity (see column 3, lines 6-14). Thus, Matuhashi *et al.* is not directed to the same type of immunogen as Marburg *et al.* and the present invention - - *i.e.* a polysaccharide derived from a pathogen conjugated to a protein carrier. Neither of the references teaches or suggests any advantage in modifying the toxin-polysaccharide combination of Matuhashi *et al.* to arrive at the presently claimed invention. There is no suggestion that Matuhashi *et al.*'s goal of decreasing the immunogenicity of the toxin would be further advanced by making the presently claimed conjugates or that any other advantage would be realized. Certainly, there is no "clear and particular" showing of a motivation to combine in either Marburg *et al.* or Matuhashi *et al.* which is required to render the present claims *prima facie* obvious.

Finally, the Examiner disregards Applicants argument that, because of the unpredictability of immunological responses to conjugates taught in the art, the skilled artisan would have had no reasonable expectation of success of boosting an immune response by conjugating the polysaccharide to two or more protein carriers. The Examiner stated that the Applicant's argument was moot since the claims do no recite any immunogenic properties. But the presently pending claims are composition claims, and such a claim need not rectie inherent properties of the claimed compositions. A composition and all of its properties are inseparable. *In re Papesch*, 137 USPQ 43 (C.C.P.A. 1963). Thus, the unexpected properties the compositions need not be recited in the claims to establish the non-obviousness of the claimed compositions.

In light of the foregoing, applicants request that the rejection of claims 1-9, 12-15 and 24 be withdrawn.

Rejection of Claims 1, 8-11 and 16-23 Pursuant To 35 U.S.C. § 103

Claims 1, 8-11 and 16-23 stand rejected pursuant to 35 U.S.C. § 103 as obvious by Marburg *et al.* and Matuhashi *et al.*, in view of Peeters *et al.* (Infection and Immunology, 1991 59(10):3504-510) teaching a dosage of less than 50 µg/dose. Applicants respectfully traverse.

Peeters *et al.* has been cited against the application as teaching the immunization of animals with a saccharide-protein conjugate of a dose less than 50 µg. (see Office Action mailed May 15, 2001). However, Peeters *et al.* fails to compensate for the deficiencies of Marburg *et al.* or Matuhashi *et al.*, as discussed above. That is, Marburg *et al.* and Matuhashi *et al.* are deficient in that the references,

alone or in combination, fail to teach or suggest every element of the presently claimed compositions, the references fail to provide motivation to combine the references, and the references offer the skilled artisan no reasonable expectation of success of achieving the claimed compositions. The teaching of Peeters *et al.* regarding the dosage of the saccharide protein conjugates fails to cure the deficiency. Consequently, Applicants respectfully request that the rejection be withdrawn.

CONCLUSION

With the above amendments and remarks, Applicants respectfully submit that the application is in condition for allowance. If the Examiner is of the opinion that a telephone conference would expedite prosecution of this matter, the Examiner is encouraged to contact Applicants' undersigned representative.

Respectfully submitted,

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